

What is claimed is:

1. A method of treating and/or providing prophylaxis against a pulmonary fungal infection, the method comprising:

5 determining the minimum inhibitory concentration of an antifungal agent for inhibiting pulmonary fungal growth; and

administering an aerosolized pharmaceutical formulation comprising the antifungal agent to the lungs of a patient;

10 wherein a sufficient amount of the pharmaceutical formulation is administered to maintain for at least one week a target antifungal agent lung concentration of at least two times the determined minimum inhibitory concentration.

2. A method according to claim 1 wherein the minimum inhibitory concentration is the minimum inhibitory concentration in the epithelial lining of the lung.

15 3. A method according to claim 1 wherein the minimum inhibitory concentration is the minimum inhibitory concentration in the solid tissue of the lung.

20 4. A method according to claim 1 wherein the target antifungal agent lung concentration is maintained for at least two weeks.

5. A method according to claim 1 wherein the target antifungal agent lung concentration is maintained for at least three weeks.

25 6. A method according to claim 1 wherein the target antifungal agent lung concentration is maintained for at least one month.

7. A method according to claim 1 wherein the target antifungal agent lung concentration is maintained for at least three months.

30 8. A method according to claim 1 wherein the administration comprises

delivering a single dose of the pharmaceutical formulation during the first week of administration.

9. A method according to claim 1 wherein the administration comprises delivering at least two doses of the pharmaceutical formulation during the first week of administration.

10. A method according to claim 1 wherein the administration comprises a first administration period and a second administration period and wherein the antifungal agent is administered more frequently or at a higher dosage during the first administration period than during the second administration period.

11. A method according to claim 1 wherein the antifungal agent is amphotericin B.

12. A method according to claim 11 wherein the target antifungal lung concentration is at least 9 $\mu\text{g/g}$.

13. A method according to claim 11 wherein the target antifungal lung concentration is a range of concentrations from 4.5 $\mu\text{g/g}$ to 20 $\mu\text{g/g}$ and wherein the administration comprises delivering the pharmaceutical formulation periodically to maintain the antifungal agent lung concentration within the target antifungal lung concentration range.

14. A method according to claim 13 wherein the target antifungal lung concentration is from 9 to 15 $\mu\text{g/g}$.

15. A method according to claim 1 wherein the antifungal agent comprises one or more of amphotericin B, nystatin, hamycin, natamycin, pimarin, ambruticin, acrisocin, aminacrine, anthralin, benanomicin A, benzoic acid, butylparaben, calcium undecyleneate, candicidin, ciclopirox olamine, cilofungin, clioquinol, clotrimazole, ecaonazole, flucanazole, flucytosine, gentian violet, griseofulvin, haloprogin, ichthammol, iodine, itraconazole, ketoconazole, voriconazole, miconazole, nikkomycin Z, potassium iodide, potassium

permanganate, pradimicin A, propylparaben, resorcinol, sodium benzoate, sodium propionate, sulconazole, terconazole, tolnaftate, triacetin, undecylenic acid, monocyte-macrophage colony stimulating factor (M-CSF), zinc undecylenate and, and pharmaceutically acceptable derivatives and salts thereof.

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16. A method according to claim 1 wherein the pharmaceutical formulation has a bulk density of less than 0.5 g/cm^3 .

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17. A method according to claim 1 wherein the pharmaceutical formulation comprises hollow and/or porous particles.

18. A method according to claim 1 wherein the pharmaceutical formulation comprises particles comprising the antifungal agent and a matrix material.

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19. A method according to claim 18 wherein the matrix material comprises one or more phospholipids.

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20. A method according to claim 1 wherein the administration comprises delivering the pharmaceutical formulation in dry powder form using a dry powder inhaler.

21. A method according to claim 1 wherein the pharmaceutical formulation comprises a propellant and wherein the administration comprises aerosolizing the antifungal agent by opening a valve to release the pharmaceutical formulation.

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22. A method according to claim 1 wherein the pharmaceutical formulation is a liquid and wherein the administration comprises aerosolizing the liquid using a compressed gas and/or a vibrating member.

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23. A method of treating and/or providing prophylaxis against a pulmonary fungal infection, the method comprising:
administering an aerosolized pharmaceutical formulation comprising

amphotericin B to the lungs of a patient;

wherein a sufficient amount of the pharmaceutical formulation is administered to maintain for at least one week a target amphotericin lung concentration of at least 5 $\mu\text{g/g}$.

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24. A method according to claim 23 wherein the amphotericin B concentration is the concentration in the epithelial lining of the lung.

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25. A method according to claim 23 wherein the amphotericin B concentration is the concentration in the solid tissue of the lung.

26. A method according to claim 23 wherein the target amphotericin B lung concentration is maintained for at least two weeks.

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27. A method according to claim 23 wherein the target amphotericin B lung concentration is maintained for at least three weeks.

28. A method according to claim 23 wherein the target amphotericin B lung concentration is maintained for at least one month.

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29. A method according to claim 23 wherein the target amphotericin B lung concentration is maintained for at least three months.

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30. A method according to claim 23 wherein the administration comprises delivering a single dose of the pharmaceutical formulation during the first week of administration.

31. A method according to claim 23 wherein the administration comprises delivering at least two doses of the pharmaceutical formulation during the first week of administration.

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32. A method according to claim 23 wherein the administration comprises a first

administration period and a second administration period and wherein the amphotericin B is administered more frequently or at a higher dosage during the first administration period than during the second administration period.

5 33. A method according to claim 23 wherein the target amphotericin B lung concentration is at least 9 $\mu\text{g/g}$.

10 34. A method according to claim 23 wherein the target amphotericin B lung concentration is a range of concentrations from 5 $\mu\text{g/g}$ to 20 $\mu\text{g/g}$ and wherein the administration comprises delivering the pharmaceutical formulation periodically to maintain the amphotericin B lung concentration within the target amphotericin B lung concentration range.

15 35. A method according to claim 23 wherein the target amphotericin B lung concentration is from 9 to 15 $\mu\text{g/g}$.

 36. A method according to claim 23 wherein the pharmaceutical formulation has a bulk density of less than 0.5 g/cm^3 .

20 37. A method according to claim 23 wherein the pharmaceutical formulation comprises hollow and/or porous particles.

 38. A method according to claim 23 wherein the pharmaceutical formulation comprises particles comprising the antifungal agent and a matrix material.

25 39. A method according to claim 38 wherein the matrix material comprises one or more phospholipids.

30 40. A method according to claim 23 wherein the administration comprises delivering the pharmaceutical formulation in dry powder form using a dry powder inhaler.

41. A method according to claim 23 wherein the pharmaceutical formulation comprises a propellant and wherein the administration comprises aerosolizing the amphotericin B by opening a valve to release the pharmaceutical formulation.

5 42. A method according to claim 23 wherein the pharmaceutical formulation is a liquid and wherein the administration comprises aerosolizing the liquid using a compressed gas and/or a vibrating member.

10 43. A method of treating or providing prophylaxis against a pulmonary lung infection, the method comprising:
determining the minimum inhibitory concentration of an antifungal agent for inhibiting pulmonary fungal growth; and
administering at least once per week an aerosolized pharmaceutical formulation comprising the antifungal agent to the lungs of a patient;
15 wherein the amount of the pharmaceutical formulation administered is sufficient to maintain for at least three weeks a target antifungal agent lung concentration that is greater than the determined minimum inhibitory concentration.

20 44. A method according to claim 43 wherein the pharmaceutical formulation is administered more than once per week for a first period and is delivered once per week for a second period.

25 45. A method according to claim 43 wherein the pharmaceutical formulation is administered once per week.

46. A method according to claim 43 wherein the minimum inhibitory concentration is the minimum inhibitory concentration in the epithelial lining of the lung.

30 47. A method according to claim 43 wherein the minimum inhibitory concentration is the minimum inhibitory concentration in the solid tissue of the lung.

48. A method according to claim 43 wherein the target antifungal agent lung concentration is maintained for at least three months.

49. A method according to claim 43 wherein the antifungal agent is amphotericin B.

50. A method according to claim 49 wherein the target antifungal lung concentration is at least 9 $\mu\text{g/g}$.

51. A method according to claim 49 wherein the target antifungal lung concentration is from 9 to 15 $\mu\text{g/g}$.

52. A method according to claim 43 wherein the antifungal agent comprises one or more of amphotericin B, nystatin, hamycin, natamycin, pimarinic, ambruticin, acrisocin, aminacrine, anthralin, benanomicin A, benzoic acid, butylparaben, calcium undecyleneate, candididin, ciclopirox olamine, cilofungin, clioquinol, clotrimazole, ecaonazole, flucanazole, flucytosine, gentian violet, griseofulvin, haloprogin, ichthammol, iodine, itraconazole, ketoconazole, voriconazole, miconazole, nikkomycin Z, potassium iodide, potassium permanganate, pradimicin A, propylparaben, resorcinol, sodium benzoate, sodium propionate, sulconazole, terconazole, tolnaftate, triacetin, undecyleneic acid, monocyte-macrophage colony stimulating factor (M-CSF), zinc undecylenateand, and pharmaceutically acceptable derivatives and salts thereof.

53. A method according to claim 43 wherein the pharmaceutical formulation has a bulk density of less than 0.5 g/cm^3 .

54. A method of treating or providing prophylaxis against a pulmonary lung infection, the method comprising:

administering at least once per week an aerosolized pharmaceutical formulation comprising amphotericin B to the lungs of a patient;

wherein the amount of the pharmaceutical formulation administered is

sufficient to maintain for at least three weeks a target amphotericin B lung concentration that is greater than the 4 $\mu\text{g/g}$.

55. A method according to claim 54 wherein the pharmaceutical formulation is administered more than once per week for a first period and is delivered once per week for a second period.

56. A method according to claim 54 wherein the pharmaceutical formulation is administered once per week.

57. A method according to claim 54 wherein the amphotericin B concentration is the concentration in the epithelial lining of the lung.

58. A method according to claim 54 wherein the amphotericin B concentration is the concentration in the solid tissue of the lung.

59. A method according to claim 54 wherein the target amphotericin B lung concentration is maintained for at least three months.

60. A method according to claim 54 wherein the target amphotericin B lung concentration is at least 9 $\mu\text{g/g}$.

61. A method according to claim 54 wherein the target amphotericin B lung concentration is from 9 to 15 $\mu\text{g/g}$.

62. A method according to claim 54 wherein the pharmaceutical formulation has a bulk density of less than 0.5 g/cm^3 .

63. A method of providing prophylaxis against a pulmonary lung infection, the method comprising:
determining the minimum inhibitory concentration of an antifungal agent for

inhibiting pulmonary fungal growth;

administering an aerosolized pharmaceutical formulation comprising the antifungal agent to the lungs of a patient, wherein the amount of the pharmaceutical formulation administered is sufficient to achieve a target antifungal agent lung concentration that is greater than the determined minimum inhibitory concentration;

thereafter administering an immunosuppressive agent to the patient for a period of time; and

maintaining the target antifungal agent lung concentration throughout the period of time.

64. A method according to claim 63 wherein the minimum inhibitory concentration is the minimum inhibitory concentration in the epithelial lining of the lung.

65. A method according to claim 63 wherein the minimum inhibitory concentration is the minimum inhibitory concentration in the solid tissue of the lung.

66. A method according to claim 63 wherein the administration comprises delivering at least two doses per week of the pharmaceutical formulation before the administration of the immunosuppressive agent and wherein the target concentration is maintained by administering doses of the pharmaceutical formulation less frequently.

67. A method according to claim 63 wherein the antifungal agent is amphotericin B.

68. A method according to claim 67 wherein the target antifungal lung concentration is at least 4.5 $\mu\text{g/g}$.

69. A method according to claim 67 wherein the target antifungal lung concentration is a range of concentrations from 4.5 $\mu\text{g/g}$ to 20 $\mu\text{g/g}$ and wherein the administration comprises delivering the pharmaceutical formulation periodically to maintain the antifungal agent lung concentration within the target antifungal lung concentration range.

70. A method according to claim 67 wherein the target antifungal lung concentration is from 9 to 15 $\mu\text{g/g}$.

5 71. A method according to claim 63 wherein the antifungal agent comprises one or more of amphotericin B, nystatin, hamycin, natamycin, pimaricin, ambruticin, acrisocin, aminacrine, anthralin, benanomicin A, benzoic acid, butylparaben, calcium undecyleneate, candididin, ciclopirox olamine, cilofungin, clioquinol, clotrimazole, ecaonazole, flucanazole, flucytosine, gentian violet, griseofulvin, haloprogin, ichthammol, iodine, itraconazole, ketoconazole, voriconazole, miconazole, nikkomycin Z, potassium iodide, potassium permanganate, pradimicin A, propylparaben, resorcinol, sodium benzoate, sodium propionate, sulconazole, terconazole, tolnaftate, triacetin, undecyleneic acid, monocyte-macrophage colony stimulating factor (M-CSF), zinc undecylenate and, and pharmaceutically acceptable derivatives and salts thereof.

15 72. A method according to claim 63 wherein the pharmaceutical formulation has a bulk density of less than 0.5 g/cm^3 .

20 73. A method according to claim 63 wherein the pharmaceutical formulation comprises hollow and/or porous particles.

74. A method according to claim 63 wherein the pharmaceutical formulation comprises particles comprising the antifungal agent and a matrix material.

25 75. A method according to claim 74 wherein the matrix material comprises one or more phospholipids.

76. A method according to claim 63 wherein the administration comprises delivering the pharmaceutical formulation in dry powder form using a dry powder inhaler.

77. A method according to claim 63 wherein the pharmaceutical formulation comprises a propellant and wherein the administration comprises aerosolizing the antifungal agent by opening a valve to release the pharmaceutical formulation.

5 78. A method according to claim 63 wherein the pharmaceutical formulation is a liquid and wherein the administration comprises aerosolizing the liquid using a compressed gas and/or a vibrating member.

10 79. A method of providing prophylaxis against a pulmonary lung infection, the method comprising:

administering an aerosolized pharmaceutical formulation comprising amphotericin B to the lungs of a patient, wherein the amount of the pharmaceutical formulation administered is sufficient to deliver at least 5 mg of amphotericin B to the lungs per week;

15 thereafter administering an immunosuppressive agent to the patient for a period of time; and

administering at least 5 mg of amphotericin B to the lungs per week throughout the period of time.

20 80. A method according to claim 79 wherein the administration comprises delivering at least 10 mg of amphotericin B before the administration of the immunosuppressive agent and delivering a lesser amount per week during the period of immunosuppression.

25 81. A method according to claim 79 wherein the amount of amphotericin B administered during the period of immunosuppression is from 5 mg to 10 mg.

82. A method according to claim 79 wherein the pharmaceutical formulation has a bulk density of less than 0.5 g/cm^3 .

30 83. A method according to claim 79 wherein the pharmaceutical formulation comprises hollow and/or porous particles.

84. A method according to claim 79 wherein the pharmaceutical formulation comprises particles comprising the antifungal agent and a matrix material.

85. A method according to claim 79 wherein the matrix material comprises one or more phospholipids.

86. A method according to claim 79 wherein the administration comprises delivering the pharmaceutical formulation in dry powder form using a dry powder inhaler.

87. A method according to claim 79 wherein the pharmaceutical formulation comprises a propellant and wherein the administration comprises aerosolizing the antifungal agent by opening a valve to release the pharmaceutical formulation.

88. A method according to claim 79 wherein the pharmaceutical formulation is a liquid and wherein the administration comprises aerosolizing the liquid using a compressed gas and/or a vibrating member.

89. A method of treating or providing prophylaxis against a pulmonary lung infection, the method comprising:
delivering an aerosolized pharmaceutical formulation comprising from 5 mg to 10 mg of amphotericin B to the respiratory tract of a patient once per week for a period of at least two weeks.

90. A method according to claim 89 wherein the pharmaceutical formulation has a bulk density of less than 0.5 g/cm^3 .

91. A method according to claim 89 wherein the pharmaceutical formulation comprises hollow and/or porous particles.

92. A method according to claim 89 wherein the pharmaceutical formulation comprises particles comprising the antifungal agent and a matrix material.

93. A method according to claim 89 wherein the matrix material comprises one or more phospholipids.

5 94. A method according to claim 89 wherein the administration comprises delivering the pharmaceutical formulation in dry powder form using a dry powder inhaler.

10 95. A method according to claim 89 wherein the pharmaceutical formulation comprises a propellant and wherein the administration comprises aerosolizing the antifungal agent by opening a valve to release the pharmaceutical formulation.

15 96. A method according to claim 89 wherein the pharmaceutical formulation is a liquid and wherein the administration comprises aerosolizing the liquid using a compressed gas and/or a vibrating member.

98. A unit dose receptacle comprising an aerosolizable pharmaceutical formulation for delivering from 5 mg to 10 mg of amphotericin B when aerosolized.